REMARKS

The February 27, 2003 Official Action and references cited therein have been carefully reviewed. In light of the amendments presented herewith, the additional experimental evidence and the following remarks, favorable reconsideration and allowance of the application are respectfully requested.

The request for continued examination has been accepted. Claims 4, 5, 16, 17, 30-38, and 65-70 are pending in the application. Claims 69 and 70, filed with the last amendment, have been withdrawn from consideration by the Examiner, because they are allegedly drawn to a different invention. Claims 4, 5, 16, 17, 30-38, and 65-68 are pending and under consideration.

First, the Examiner has objected to claims 4, 5, 16, 17, 30-38, and 65-68 as improperly dependent because they depend from cancelled claims. The above-mentioned claims have also been rejected under 35 U.S.C. §112, second paragraph as lacking proper antecedent basis. Claims 4, 5, 16, 17, 30-38 and 65-68 have been amended such that they properly depend from a pending claim thereby overcoming the foregoing objection and rejection.

Next, the Examiner has maintained the rejection of claims 4, 5, 16, 17, 30-38, and 65-68 under 35 U.S.C. §112, first paragraph asserting that the skilled person would have to perform undue experimentation to practice the invention claimed.

The foregoing constitutes the entirety of the objections and rejections raised in the February 27, 2003 Official Action. In light of the present claim amendments and the following remarks, each of the above-noted rejections under 35 U.S.C. § 112, first and second paragraph are respectfully traversed.

CLAIMS 4, 5, 16, 17, 30-34, 36-38, AND 65-68 AS AMENDED ARE FULLY ENABLED BY THE SPECIFICATION AS FILED

Claims 4, 5, 16, 17, 30-38, and 65-68 have been rejected under 35 U.S.C. §112, first paragraph because the claims allegedly contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or which it is most nearly connected to make and/or use the invention.

The standards for enablement are well established: As noted in the MPEP at § 2164,

> The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention.

In § 2164.01, the MPEP continues,

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.
> (*Quoting United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

The test for enablement is the balancing of several specifically prescribed factors listed in MPEP § 2164.01(a), as follows:

> These factors include, but are not limited to:
>
> (A) The breadth of the claims;
> (B) The nature of the invention;
> (C) The state of the prior art;
> (D) The level of one of ordinary skill;
> (E) The level of predictability in the art;
> (F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In general, it is the Examiner's position that it would require undue experimentation for one skilled in the art to practice the invention. Applicants respectfully disagree.

The MPEP clearly sets forth that experimentation is permitted in an enabled invention, provided that experimentation is merely routine. See MPEP 2164.06:

> "The quantity of Experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F2.d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(citing *In re Angstadt*, 537 F.2d 489, 502-4, 190 USPQ 214, 217-219 (CCPA 1976))."

It is respectfully submitted that in the instant case, the experimentation required is merely routine, and extensive guidance for the practice of the invention is provided in the specification. For example, at pages 11-12 of the specification as originally filed, the HERG gene is described, as is the HERG gene A561V mutation. This mutation is known and disclosed to produce a defective potassium channel rectifier, which interferes with the WT HERG potassium channel rectifier in a dominant negative manner. Expression of A516V HERG mutant in

cardiomyocytes inhibits K+ current through the HERG membrane protein, and delays myocardial conduction. This is the same mechanism by which ibutilide, an art standard treatment for re-entrant arrhythmias acts. Thus the instant specification discloses the explicit mechanism of cardiac re-entrant arrhythmias, and provides a treatment which acts by the same mechanism as the art known treatment.

The specification also provides guidance for alternative means of treating re-entrant atrial flutter, and for treatment of other disorders, using reverse gene therapy. For example, at pages 13-14, alternate reverse gene therapy targets for treating re-entrant atrial flutter are disclosed. At pages 16-18 guidance for selecting and utilizing other specific genes for reverse gene therapy treatment of specific corresponding disorders are discussed.

Moreover, the specification provides explicit guidance regarding exemplification of methods of making and using the invention. All of the examples provide this guidance, particularly in Example 3, which describes a method of administering mutant HERG to treat re-entrant arrhythmias. Therefor, applicants submit that the guidance provided in the specification as originally filed is sufficient that one skilled in the art could practice the invention without undue experimentation.

Finally, the Examiner is reminded of the evidence submitted in the previously submitted Supplemental response of March 5, 2002. The data presented showed that plasmid encoding a mutant HERG protein correctly localized to the pig myocardium in vivo and also influenced the biophysical function of the K+ channel in HEK293 cells.

The Examiner raises specific issues with regard to enablement, which are each addressed individually below.

First, the Examiner argues that in order to utilize the invention in the treatment of a particular disease, knowledge of the mechanism underlying the disease must be known. Accordingly, it appears to be the Examiner's position that the claims should be limited to administering mutant HERG to treat re-entrant cardiac arrhythmia.

While applicants concur that knowledge of the mechanism of a disease is preferable, it is not required. Correction of an aberrant phenotype by a reverse gene therapy vector of the invention can be achieved without a clear understanding of the mechanism underlying the disease state. The skilled person is well aware of techniques for assessing restoration of normal cellular functions. Nonetheless, in the interest of expediting prosecution, applicants have amended the claims so that they are clearly drawn to treating re-entrant arrhythmias by administering a defective HERG protein.

Next, the Examiner argues that use of HERG to treat cardiac arrhythmia is not predictable. In support of this argument, the Examiner re-cites Sanguinetti et al., and Kagan et al., stating that they show that the effect of mutant HERG on re-entrant atrial flutter is not predictable until the actual effect is shown. The Examiner further cites Bradley et al. as allegedly showing that overexpression of the normal HERG gene in ventricular myocytes suppresses cardiac hyperexcitability (see page 6 of the official action.)

With regard to Sanguetti et al., the Examiner indicates that Sanguetti et al. (Cell (1995) 81:299-307) teaches that "Interestingly, HERG current is not blocked by drugs that specifically block I_{KR} in cardiac myocytes..." and argues that this indicates a lack of predictability of the effect of mutant HERG on re-entrant atrial flutter. Applicants respectfully submit that this citation is misleading for two reasons. First,

the quote cited by the Examiner is pulled from the abstract, and is a generalization of the teachings of Sanguetti et al. The discussion section of Sanguetti et al. provides more explicit information about the nature of HERG and mutant HERG activity. This section indicates that "HERG encodes the major subunits of the cardiac I_{KR} channel...." and that "The only major difference between HERG current and I_{KR} is that HERG is not blocked by methanesulfonanilide drugs...This suggests that the I_{KR} and the methanesulfonanilide receptor are separate, but interacting channels." Thus the paper does not question the effect of defective HERG, but rather indicates that there are other means of blocking K^+ conduction. This would in no way impair the dominant negative regulation of K^+ conduction by HERG. Further in evidence of the same, later work by Sanguetti et al., published prior to the instant application's filing date (Sanguetti et al., PNAS (1996) 93:2208-2212, submitted in the IDS filed June 20, 2000), provides extensive guidance regarding the dominant negative nature of many HERG mutations, including A561V, and their effect on K^+ conduction. From these teachings, it is clear that the A561V HERG mutation produces suppression of HERG channel function, which reduces net-repolarization current, and lengthens the duration of cardiac action potentials (see discussion section.) This is the effect sought to treat re-entrant arrhythmia.

The Examiner also cites Kagan et al. as allegedly teaching a lack of predictability of the effect of mutant HERG on myocardial conduction. Specifically, the Examiner notes in paper #11, that "while Kagan et al. support that there may be some correlation between HERG A561V expression and reducing wild type current density...Kagan et al do not provide any evidence that such expression levels *in vitro* would be correlative to achieving therapeutic effects in a subject..." Applicants submit that

contrary to the Examiner's position, the explicit effects taught by Kagan et al. *in vitro*, are direct evidence of the claimed therapeutic effect in a subject. The reference cited by the Examiner teaches that the effect instantly encompassed by the claims has a predictable result *in vitro*. Absent evidence to the contrary, this effect would be expected in a test subject as well. The Examiner has provided no evidence to teach or suggest that this effect would not also be expected *in vitro*. *In vitro* evidence is presumed to correlate to *in vivo* effect, absent evidence to the contrary. (MPEP 2164.02)

> "...if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):
>
> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)"

In the instant case, the specification as filed extensively describes the mechanism of delivering mutant HERG for the treatment of re-entrant cardiac arrhythmias, as well as various models which correlate well to such treatment methods (in

cardiomyocytes and in canine animal models, both discussed in the background and exemplified in the Examples.) The Examiner has provided no evidence which refutes the suitability of these models, and as set forth above, it is the Examiner's burden to set forth evidence that the models would not correlate well to the desired therapeutic effect. As described above, art cited by the Examiner as allegedly demonstrating a lack of correlation does not in fact teach such.

Finally, with regard to Ness et al. (cited as Bradley by the Examiner), the Examiner indicates that this reference teaches that overexpression of normal HERG suppresses cardiac hyperexcitability. According to the Examiner, this provides a lack of predictability to the instant invention which indicates that expression of defective HERG produces the same effect. Applicants respectfully submit while both Ness et al. and the instant invention both teach a means of reducing cardiac hyperexcitability, the cause of the hyperexcitability is different in each case. Ness et al. aim to treat a cardiac condition caused by abnormalities in repolarization, while the instant invention aims to treat a cardiac arrhythmia caused by tachyarrthmic conduction circuits (see specification page 11.) These are distinct and opposite causes of cardiac hyperexictability.

Thus Ness et al. teach that overexpression of HERG enhances repolarization, and thus suppresses phase 2 EAD (early active depolarization) and increases the refractory period. Contrarily, the aim of the instant invention is to delay myocardial conduction, including repolarization, in order to treat arrhythmias caused by tachyarrthmic conduction circuits. All of the references cited concur in teaching that overexpressing HERG improves myocardial conduction, and that mutant HERG decreases the same. Thus contrary to the Examiner's generalization,

overexpression of HERG does not have the same effect as expression of mutant HERG.

The Examiner further argues that the reasoning for the lack of predictability *in vivo* was set forth in paper #22, wherein the delivery of a dysfunctional gene and delivery of the same did not bring a therapeutic effect for gene therapy of diabetes and cystic fibrosis. In support of this generalization, the Examiner cites Boucher et al., Eck et al., and Alton et al. However these references are all drawn to administration of a functional version of a gene to supplement a patient's non-functioning gene. This is distinct from the instant invention, which seeks to administer a gene product which is normally only expressed in abnormal tissue not affected by the disease or disorder. These references are all drawn to traditional gene therapy (where a functional gene is administered to supplement the activity of a non-functional gene.) Applicants submit that while the invention is similar to traditional gene therapy, it is certainly not identical, and thus direct comparisons between the two are improper. In the instant case, a dysfunctional gene which is unrelated to the dysfunction gene responsible for the patient's disorder is administered to a specific tissue, where it's usually undesirable effect ameliorates disease symptoms. The instant invention is supplied to provide solutions to some of the pitfalls of gene therapy (see the background section at pages 2-3, which extensively describe the problems previously associated with gene therapy, and how the instant invention OVERCOMES these problems.

Additionally, the Examiner argues that the evidence provided in the Supplemental response submitted by applicant on March 5, 2002 which demonstrates inhibition of potassium conduction *in vitro*, and expression of mutant potassium channels *in vivo* was also insufficient to provide evidence that the disclosure is

enabling, since an *in vivo* therapeutic effect has allegedly still not been shown. In response to this assertion, submitted herewith are a series of graphs showing that administration of a mutant HERG, Q9E MiRP-1, to pig myocardium in a reverse gene therapy vector of the invention functions to induce waveform changes and prolongation of the atrial epicardial monophasic action potential duration in pigs due to a clarithromycin infusion. This data provides the in vivo effect required by the Examiner. Applicants intend to supplement this response with a Rule 132 Declaration by Dr. Levy in order to further describe this data to the Examiner.

In summary, the specification provides extensive guidance to the skilled person, a description of the underlying disease mechanism, and materials and methods for effecting reverse gene therapy for the treatment of cardiac arrthymias. The *in vitro* and *in vivo* data supplied during the prosecution of the present application demonstrates a clear correlation between in vivo and in vitro therapeutic effects. In light of all the foregoing, it cannot be reasonably maintained that undue experimentation would be required to practice the invention as presently claimed.

In light of the foregoing claim amendments, experimental evidence and remarks, Applicants respectfully submit that the claims as amended comply with all the requirements of 35 U.S.C. §112, first paragraph and request that the rejection of the claims under 35 U.S.C. §112, first paragraph be withdrawn.

CONCLUSION

It is respectfully urged that the rejections set forth in the February 27, 2003 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone

interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

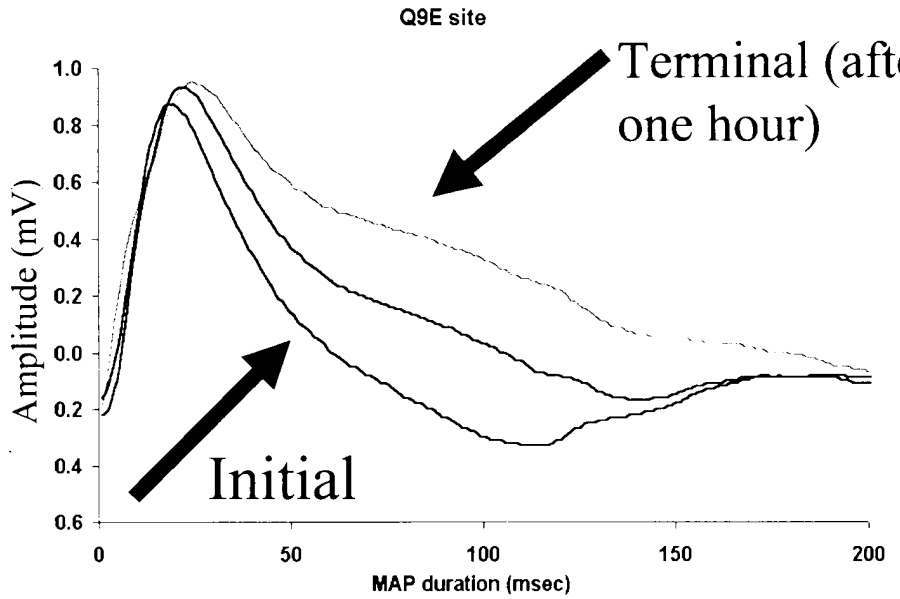
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By 
Kathleen D. Rigaut, Ph.D., J.D.
PTO Registration No. 43,047

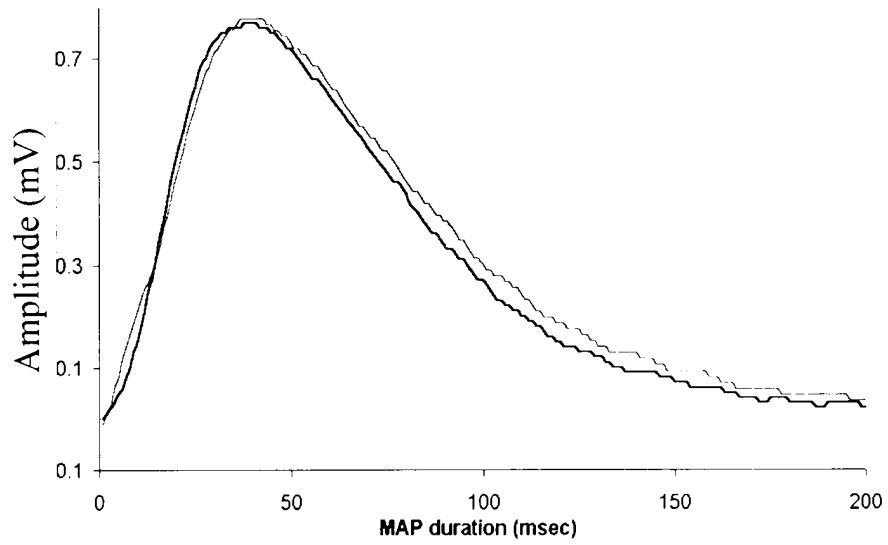
Telephone: (215) 563-4100
Facsimile: (215) 563-4044
Enclosures: Data showing efficacy of reverse gene therapy in vivo

An example of the waveform changes and prolongation of the atrial epicardial monophasic action potential (MAP) duration in pigs due to a clarithromycin infusion in Q9E transfected atrial myocardium compared to wild type (WT) which shows minimal change.

Q9E MiRP-1



Controls: WT or shame



MAP (mean±se) prolongation in pig atriumduring clarithromycin infusions (n=6)